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(21) International Application Number: PCT/GB99/02831 (22) International Filing Date: 10 September 1999 (10.09.99) (30) Priority Data: 9819685.0 10 September 1998 (10.09.98) GB (71) Applicant (for all designated States except US): NORTON HEALTHCARE LTD. [GB/GB]; Albert Basin, Royal Docks, London E16 2QJ (GB). (72) Inventor; and (75) Inventor/Applicant (for US only): WOOLFE, Austen, John [GB/GB]; 31 Emberson Way, North Weald, Essex CM19 6DL (GB). (74) Agent: BROWNE, Robin, Forsythe; Urquhart-Dykes & Lord, Tower House, Merriion Way, Leeds LS2 8PA (GB).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: ANTI-INFLAMMATORY PHARMACEUTICAL FORMULATIONS		
(57) Abstract An oral pharmaceutical dosage form including a mixture of a delay release formulation of a non-steroidal anti-inflammatory drug (NSAID) and a mixture containing a prostaglandin and one or more excipients.		

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ANTI-INFLAMMATORY PHARMACEUTICAL FORMULATIONS

This invention relates to pharmaceutical formulations of anti-inflammatory drugs, particularly non-steroidal anti-inflammatory drugs (NSAIDs).

These NSAIDs are used for the treatment of inflammatory conditions such as osteoarthritis or rheumatoid arthritis. A side effect of the oral administration of NSAIDs particularly with long term usage, is a liability to ulcerogenic effects. NSAID induced ulcers in the stomach are potentially dangerous because few or no symptoms may be detected until significant damage has been caused. Certain prostaglandins, for example misoprostol have been shown to reduce and even prevent such ulcers.

Various patent applications relate to use of misoprostol with immediate release drugs, for example GB-A-2135881 (Farmitalia Carlo Erba), WO91/16896 (G D Searle), or where a gastric resistant coating is put over the NSAID in an attempt to reduce further gastric erosion due to release in the stomach of the NSAID, for example WO91/16895, WO91/16886 (G D Searle).

There is an increasing use of sustained release preparations of NSAID drugs to reduce the number of doses required by the patient each day. Although the theory of such preparations is that the majority of the drug is released in the intestine rather than the stomach, in practice there is a significant occurrence of gastric problems. This may be due to release of small amounts of drug within the stomach.

The incorporation of misoprostol into such products to reduce the potential for such problems has not previously been disclosed.

According to the present invention an oral pharmaceutical dosage form includes a mixture of a delay

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release formulation of a NSAID and a mixture containing one or more excipients and a prostaglandin.

The delay release NSAID formulation preferably comprises coated beads or pellets.

The prostaglandin mixture may be provided in the form - of a powder which is mixed with the NSAID formulation within the dosage form.

The dosage form may comprise a tablet, capsule, granule or other commonly used configuration. However preferred dosage forms comprise a capsule containing multi-particulate beads of the NSAID formulation together with the powdered prostaglandin mixture. The NSAID beads preferably have coatings adapted to provide programmed release according to the position in the gastrointestinal tract. Use of such beads provides a more repeatable release along the gastrointestinal tract and may reduce gastric erosion because the small pellets or beads are easily moved and do not adhere readily to the folds of the gastric wall.

Beads for use in accordance with this invention may have a single slowly erodible coat or may comprise mixtures of beads with differing levels or types of coating adapted to provide a continuous or distributed release profile through the gastrointestinal tract. The delay afforded may range from a minimal delay to several hours, dependent on the pH of the gastrointestinal tract in the immediate vicinity.

The NSAID is preferably but not exclusively one of reasonably low weight per standard dose, that is 200 mg or below. Examples of suitable NSAIDs include tiaprofenic acid, piroxicam, flubiprofen, tenoxicam, meloxicam or similar molecules. Salts or other derivatives of these drugs may be employed in a conventional manner. Most preferably the drug is diclofenac sodium, ketoprofen or indomethacin. Mixtures may be used.

It is possible to produce the pellets or beads by conventional means. Techniques that can be used can include

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coating the drug on a non-pariel core preferably composed of inert sugar or similar substance and then overcoating with the required coating before encapsulation. The following steps may be employed.

- i. Preparation of inert core by conventional pan coating method.
- ii. Active coating by using rotary type fluidized bed.
- iii. Protective coating by using rotary type fluidized bed.
- iv. Enteric coating by using rotary type fluidized bed.

The procedure disclosed in EP-A-519144 may be used.

Drug delivery using capsules avoids a further compression step as may be necessary during tablet manufacture.

An alternative method is to form beads or pellets by co-acervation or alternatively by precipitation from solution as described by Zaniboni, Fell and Collett, (Int.J.Pharm, 1995, 125, 151-5).

In a preferred technique the beads may be formed by spheronisation, rotogranulation or a similar technique. If tablets are to be made, preferably the beads should be soft enough to deform slightly under compression to avoid cracking but not too soft so as to deform significantly as deformation may also cause cracking or rupture of the coat. A mixture of drug with a suitable amount of an excipient or excipients can be found by simple experiments. Suitable excipients include polyvinyl pyrrolidone, sugars and cellulose derivatives particularly microcrystalline cellulose.

The coating for the beads may include cellulose derivatives eg hydroxypropyl methyl cellulose, methacrylic acid and derivatives eg methyl methacrylates for example, Eudragrit® (Rhom Pharma), especially Eudragrit L or S. Other standard enteric coating materials may be used for example

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phthalates, eg cellulose acetate phthalate or preferably hydroxypropylacetate phthalate or polyvinylacetate phthalate. Mixtures of these and other materials may be used to produce delay release coated beads. Normally the coating will include plasticisers eg polyethylene glycol, triacilin or - phthalate esters.

The prostaglandin component preferably contains misoprostol optionally together with one or more inert excipients. The prostaglandin is normally provided as a 1:10 or 1:100 dilution on an inert cellulose or other binder or filler. Especially useful materials for this invention is hydroxypropyl methyl cellulose. The dosage of prostaglandin may be chosen to be suitable to prevent or reduce stomach ulceration caused by the NSAID. A suitable dose of misoprostol is between 10 - 500 μ g preferably 50 - 200 μ g per dosage form but this may be increased or decreased depending on the NSAID used.

Preferred dosage forms comprise capsules, preferably hard gelatin capsules.

In preferred embodiments of the invention, the potential for gastric erosion is reduced by ensuring that the prostaglandin is released before the NSAID. Any beads for immediate or rapid release are coated with an inert coating which defer solubility in gastric fluid, for example for a period of 30 minutes. Such materials include cellulose derivatives for example hydroxypropyl methyl cellulose, methyl or ethyl celluloses or other sealants eg Zein. Thin coatings of methacrylate derivatives e.g. polyhydroxymethacrylate or other materials such as hardened gelatine, waxes, starches or polyvinyl pyrrolidone may be used. Other portions of the beads may be coated with methacrylate derivatives, phthalates, for example hydroxypropyl methyl cellulose phthalate or similar materials to give an appropriate release profile as is well known in the art.

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The invention is further described by means of example, but not in any limitation sense.

Example 1

Hard gelatin capsules fill ws prepared containing a - mixture of the following:

delay release ketoprofen beads	250mg
misoprostol	
(diluted 1:100 on hydroxypropylmethylcellulose)	20mg
lactose (anhydrous)	160mg
hydrogenated vegetable oil	4mg

The beads were prepared by spray coating a suspension or solution of ketoprofen onto a non-pareil sugar core, together with a binder e.g. polyvinylpyrrolidone or hydroxypropylmethyl cellulose. The beads were subsequently coated with a delay release coating e.g. methylmethacrylate (e.g. Eudragit (Trade Mark)). Mixtures of beads with various levels of coating were used to give the required therapeutic release pattern.

In a fluidized bed apparatus, uniform spherical inert sugar sphere cores were coated with a first layer consisting of the compounds, an inert water soluble polymer such as hydroxy-propylmethylcellulose or hydroxypropylcellulose, and talc. The second layer consisted of an inert water soluble polymer such as hydroxypropylmethylcellulose or hydroxypropylcellulose, talc and a pigment such as titanium dioxide. The third and enteric coating layer consisted of an enteric coating polymer such as co-polymerized methacrylic acid / methacrylic acid methyl esters, a plasticiser such as triethylitrate or similar plasticisers, and talc.

The layers were applied by conventional fluidised bed coating techniques using aqueous solutions or dispersions.

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Pseudo zero release was obtained by use of a mixture of beads released at various pH's or at various times dependent on the type of coating.

The beads in Example 1 contained 40% ketoprofen giving a dose per capsule of 100mg plus 100µg misoprostol. -

The mix was then filled into suitable hard gelatine capsules.

Example 2

The following formulation was employed:

delay release diclofenac beads	214mg
microcrystalline cellulose (dried)	150mg
e.g. Avicel R PH112	
misoprostol (1 in 100 dilution on HPMC)	20MG
stearic acid	4mg
talc	8mg

Beads containing 35% diclofenac sodium i.e. 75mg drug per dose were prepared.

The beads were formed as previously described, or by mixing with a bulking agent e.g. microcrystalline cellulose, moistening with water, extruding and spheronising to give spherical or ovoid particles about 0.5mm to 1.5mm in diameter. These were dried and coated as previously described using a standard coating agent. The beads were mixed as required to give the required release profile.

The beads are usually provided with a coating to prevent immediate release in the stomach, particularly release before the misoprostol has dissolved.

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CLAIMS:

1. An oral pharmaceutical dosage form including a mixture of a delay release formulation of a non-steroidal anti-inflammatory drug (NSAID) and a mixture containing a prostaglandin and one or more excipients.
2. A dosage form as claimed in claim 1 wherein the NSAID formulation comprises coated pellets or beads.
3. A dosage form as claimed in claim 1 or claim 2, wherein the prostaglandin is misoprostol.
4. A dosage form as claimed in any preceding claim, wherein the prostaglandin mixture is a powder.
5. A dosage form as claimed in any preceding claim comprising a capsule containing multi-particulate beads of the NSAID formulation together with the powdered prostoglandin mixture.
6. A dosage form as claimed in any of claims 2 to 5 comprising a mixture of beads with different levels or types of coating.
7. A dosage form as claimed in any preceding claim wherein the NSAID is selected from the group consisting of tiaprofenic acid, piroxicam, flubiprofen, tenoxicam, meloxicam and salts and derivatives thereof.
8. A dosage form as claimed in claim 7 wherein the NSAID is selected from the group consisting of diclofenac sodium, ketoprofen and indomethacin and mixtures thereof.

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9. A dosage form as claimed in any of claims 2 to 7, wherein the dosage of misoprostol is 50 to 200 μ g per dosage form.
10. A dosage form as claimed in any of claims 2 to 9 - wherein the pellets or beads comprise coatings including the drug on non-preil cores.
11. A dosage form as claimed in any of claims 2 to 8 wherein the pellets or beads are made by co-acervation or precipitation from solution.
12. A dosage form as claimed in claim 10 wherein the beads are made by spheronisation or rotogranulation.
13. A dosage form as claimed in any of claims 10 to 12 wherein the coating includes the drug and an excipient selected from the group consisting of: polyvinyl pyrrolidone, sugars and cellulose derivatives.
14. A dosage form as claimed in any of claims 2 to 13 wherein the pellets or beads have a coating of compounds selected from the group consisting of: hydroxypropyl methyl cellulose, methacrylic acid and derivatives, methyl methacrylates, cellulose acetate phthalate, hydroxypropylacetate phthalate, polyvinylacetate phthalate and mixtures thereof.
15. A dosage form as claimed in claim 14 wherein the coating includes a plasticiser selected from the group consisting of: polyethylene glycol, triacilin or phthalate esters.
16. A dosage form as claimed in any preceding claim comprising a filled hard gelatine capsule.

INTERNATIONAL SEARCH REPORT

Int. National Application No.

PCT/GB 99/02831

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/50 A61K31/557

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 91 16895 A (G.D. SEARLE) 14 November 1991 (1991-11-14) cited in the application	1-3, 7-16
Y	claims 1-3, 9-12	4-6
Y	US 5 232 704 A (G. D. SEARLE) 3 August 1993 (1993-08-03) claims 1, 8, 9	4-6
P, X	WO 99 12524 A (NYCOMED DANMARK) 18 March 1999 (1999-03-18) claims 1, 6, 7, 11, 16, 18 page 34, line 20 - page 39, line 17	1-16

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Information on patent family members

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